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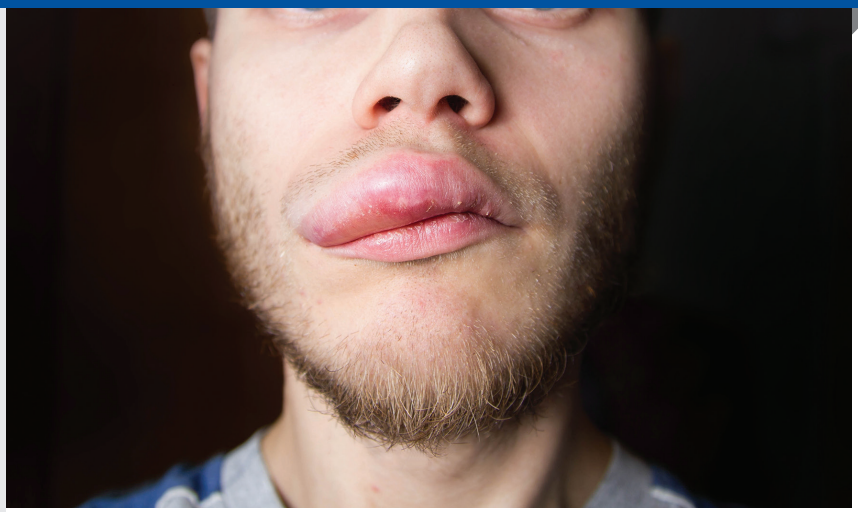
Emergency Medicine Practice
Evidence-Based Education • Practical Application

CLINICAL CHALLENGES:

- **What are the main categories of angioedema** and how will patients present in the ED?
- **How can you assess the risk** for airway compromise?
- **Which pharmacologic treatments** are recommended for angioedema?



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Prior to beginning this activity, see "CME Information" on page 2.

Angioedema in the Emergency Department: An Evidence-Based Update

Abstract

Angioedema is a histamine- or bradykinin-mediated response that can be acquired, hereditary, or idiopathic. Manifestations include nonpitting edema of the subcutaneous layer of the skin or submucosal layers of the respiratory or gastrointestinal tracts. While acute presentations are typically transient and localized, angioedema can result in acute airway compromise, requiring immediate stabilization. It can also result in abdominal pain that is commonly misdiagnosed, resulting in unnecessary and potentially harmful procedures. This review assesses current literature on the etiology and management of angioedema in the emergency department. An analysis of the most recent evidence on therapeutic options is provided, while addressing barriers to use.

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) identify areas in practice that require modification to be consistent with current evidence in order to improve competence and performance; (2) develop strategies to accurately diagnose and treat both common and critical ED presentations; and (3) demonstrate informed medical decision-making based on the strongest clinical evidence.

CME Objectives: Upon completion of this activity, you should be able to: (1) describe the pathophysiology of the various types of angioedema; (2) assess and evaluate a patient with undifferentiated angioedema; (3) select the optimal therapeutic agent, based on the source of angioedema; and (4) determine the proper disposition of patients with acute angioedema

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Case Presentations

CASE 1

A 23-year-old man presents by EMS with abdominal pain…

- The patient reports that for the past 4 hours he has had generalized abdominal pain that is sharp, constant, and increasing in intensity. He has associated nausea and nonbloody emesis. He denies fever, back pain, urinary complaints, chest pain, shortness of breath, or penile discharge. He denies recent NSAID, antibiotic, or drug or alcohol use, as well as recent travel or sick contacts. He states his father's lips occasionally swell but does not know any other details of the condition. He does report having multiple similar occurrences of this abdominal pain, but with negative lab testing and imaging.
- His vital signs are: temperature, 36.6C°; heart rate, 112 beats/min; blood pressure, 104/70 mm Hg; respiratory rate, 22 breaths/min; and oxygen saturation, 100% on room air.
- His abdomen is soft, moderately distended, and diffusely tender to palpation without guarding or rebound. His genital exam is unremarkable. You are concerned for a surgical abdomen, but the recurrent nature of the presentation makes you suspicious that something else is going on…

CASE 2

A 48-year-old woman presents to the ED with lip swelling…

- She states her lips felt "heavy" when she woke up this morning, but over the past 8 hours, she has noticed significant swelling. She denies shortness of breath, voice change, rash, or prior history of similar occurrences, as well as fever or infection, any known allergies, or significant family history. She said she has had no recent exposures, travel, or trauma.
- The patient's past medical history includes hypertension, diabetes mellitus type 2, and hyperlipidemia. She reports that she currently takes lisinopril, metformin, and atorvastatin.
- Her vital signs are: temperature, 37C°; heart rate, 82 beats/min; blood pressure, 138/78 mm Hg; respiratory rate, 16 breaths/min; and oxygen saturation, 100% on room air.
- On examination, the patient is in no distress, but she has significant upper and lower lip swelling, with no oropharyngeal involvement. The rest of her examination is unremarkable. You wonder whether her condition will progress and whether you should administer corticosteroids and antihistamines and proactively intubate her…

Introduction

Angioedema is a physical manifestation of a variety of disease processes. It results when excessive histamine is released during mast cell degranulation or from processes that result in excessive bradykinin formation. Clinically, angioedema presents as transient, localized, nonpitting swelling of the subcutaneous layer of the skin or submucosal layer of the respiratory or gastrointestinal tracts. It can be acute or chronic, acquired or hereditary. It occurs along a spectrum and can be a manifestation of anaphylactoid-type reactions. While the all-cause incidence of angioedema is unknown, approximately 110,000 emergency department (ED) visits in the United States are coded as angioedema.[1]

Understanding of the various etiologies and presentations of angioedema is key to management, which is underscored by the fact that up to 44% of patients with hereditary angioedema (HAE) are initially misdiagnosed.[2] Advances in therapeutics offer new management options for the treatment of angioedema; however, new therapies are expensive and must be selected judiciously for the appropriate patient. In this issue of *Emergency Medicine Practice*, the initial management and stabilization of patients presenting with angioedema are discussed as well as the various causes, diagnostic measures, and treatment strategies available.

Critical Appraisal of the Literature

A literature search was performed using MEDLINE® Epub, MEDLINE® In-Process, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from 1999 to present, using the search terms *angioedema* and *emergency department*. The search was limited to English-language articles that were systematic reviews, meta-analyses, multicenter studies, clinical trials, or randomized controlled trials. Using this approach, 730 articles were screened, and ultimately 86 were included in this review.

There is a high level of evidence in the literature pertaining to the pathophysiology, diagnostic studies, and initial management of angioedema. There are a limited number of studies evaluating ED use of targeted therapies for acute angioedema, but the studies conducted appear to have minimal bias and appropriate study design.

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Etiology and Pathophysiology

Angioedema occurs secondary to vasodilation and increased tissue permeability, leading to interstitial edema. Angioedema can be broadly classified into 3 categories: (1) histamine-mediated, (2) bradykinin-mediated, and (3) idiopathic.[3] The underlying pathophysiology drives the clinical presentation and treatment considerations. Histamine-mediated angioedema typically has a rapid onset with associated urticaria, while bradykinin-mediated angioedema is frequently more severe and longer-lasting, but does not usually manifest urticaria.[4]

Histamine-Mediated Angioedema

Histamine-mediated angioedema is the most common form of angioedema, accounting for 40% to 70% of ED presentations. Histamine-mediated angioedema exists along the spectrum of allergic reaction and anaphylaxis.[5] It may be associated with urticaria and pruritus, and often progresses very quickly. There are 3 pathways leading to histamine-mediated angioedema:[6]

- Immunoglobulin E type I hypersensitivity reactions (eg, triggered by environmental allergens, foods, insect stings)
- Direct mast cell degranulation (eg, triggered by radiocontrast media or opioids)
- Inhibition of cyclo-oxygenase 1 and 2 (eg, triggered by nonsteroidal anti-inflammatory drugs [NSAIDs]).

Final activation of the histamine H1 and H2 receptors (along with other vasoactive peptides) is responsible for interstitial edema.[7] Physically induced angioedema caused by cold, pressure, vibration, or ultraviolet radiation is generally considered to be histamine-mediated.[8]

Bradykinin-Mediated Angioedema

Bradykinin binds to the bradykinin B1 and B2 receptors on vascular endothelial cells, leading to destruction of vascular endothelial cell cadherin. This leads to edema via water movement from the vascular space to the extracellular space.[9] Bradykinin is regulated by several systems, including the coagulation, complement, and contact pathways, which interact with the kallikrein-kinin system, and dysfunction at multiple steps can lead to angioedema via excess production or release of bradykinin, or via inhibition of bradykinin breakdown. C1 esterase inhibitor (C1-INH) is a key inhibitor of multiple steps of the cascade leading to bradykinin production.

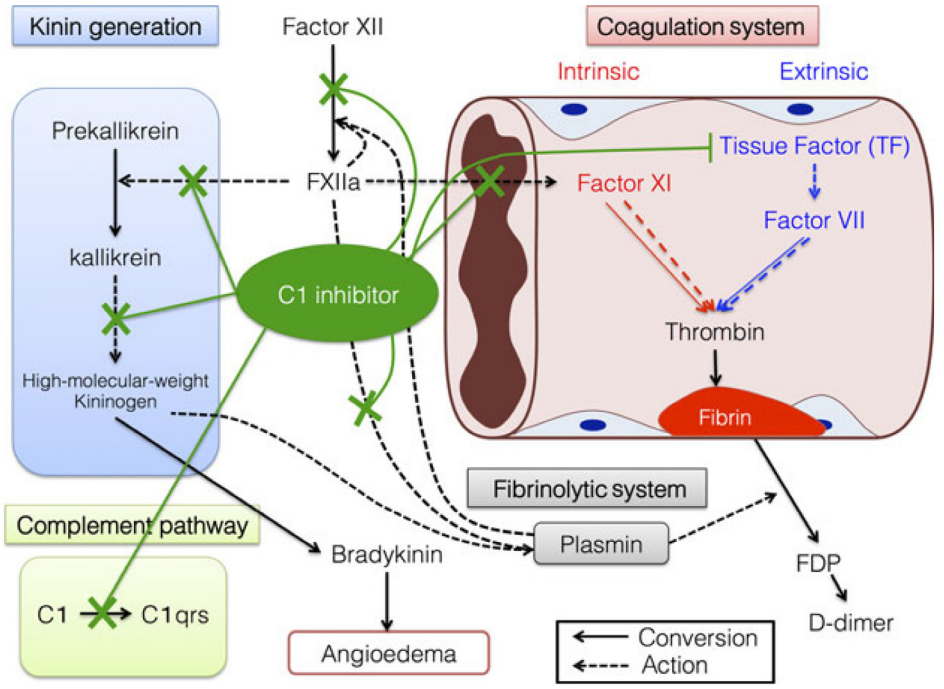
The contact system consists of protein factor XII (Hageman factor), prekallikrein, high-molecular-weight kininogen (HMWK), and factor XI. Activation of the contact system begins with activation of factor XII, which cleaves prekallikrein to free kallikrein. Kallikrein then activates additional factor XII and frees bradykinin from HMWK. C1-INH stabilizes the prekallikrein-HMWK complex, thus preventing bradykinin formation. C1-INH also functions to inhibit the classical complement pathway. Deficiency of C1-INH leads to reduced C2 and C4 levels.[10] **(See Figure 1.)**

These forms of angioedema are not associated with urticaria, are not triggered by an allergic reaction, and may progress slowly over hours to days.[11] Bradykinin-mediated angioedema subtypes include HAE, acquired angioedema (AAE), angiotensin-converting enzyme (ACE)-inhibitor-induced angioedema, and tissue plasminogen activator (tPA)-induced angioedema. These are summarized in following sections.

Hereditary Angioedema

HAE has several subtypes, but type 1 and type 2 are the most common, with a reported prevalence between 1:100,000 and 1:150,000.[12] Type 1 stems from a deficient level of C1-INH, while type 2 stems

Figure 1. Pathways Inhibited by C1 Esterase Inhibitor



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from decreased C1-INH function.[13] Approximately 25% of HAE cases arise from de novo mutations and will thus not have a positive family history.[14] Type 3 HAE (or HAE with normal C1-INH) is related to mutations in coagulation factor XII.

Acquired Angioedema

Acquired angioedema (AAE) is caused by an acquired C1-INH deficiency and is a very rare condition, with an estimated prevalence of 1.5 per 1,000,000.[15] A hematologic disorder such as monoclonal gammopathy of uncertain significance or B-cell malignancies are present in most cases.[16]

Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema

ACEI use is a well-identified cause of angioedema. Up to 30% of all ED visits for angioedema in the United States are caused by an ACEI.[11] The angiotensin-converting enzyme (ACE) is involved in the breakdown of bradykinin; thus, inhibiting ACE also results in an increased level of bradykinin.[14] Note that this is not an allergic reaction to the ACEI but, rather, a side-effect. ACEI-induced angioedema is a class effect and is not dose-dependent, so symptoms can occur any time from a few hours to up to 10 years after the initial dose.[17] Approximately 0.7% of patients develop angioedema within 5 years of ACEI use.[18]

Tissue Plasminogen Activator-Induced Angioedema

Alteplase, a tissue plasminogen activator (tPA), has been shown to increase kinins in plasma.[19] The incidence of AAE after alteplase administration is reported to be between 0.9% and 7.9%.[20]

Idiopathic Angioedema

Idiopathic angioedema may be histamine-mediated or bradykinin-mediated. Mechanisms are thought to be similar to those described previously, and cases are classified as idiopathic histamine-mediated if the patient clinically responds to antihistamines and a workup for bradykinin-mediated etiology is negative. Idiopathic angioedema is classified as possibly bradykinin-mediated if the patient is clinically unresponsive to high-dose antihistamines.[5]

Differential Diagnosis

Angioedema can have a wide range of presentations, which can make formal diagnosis difficult in the ED. Frameworks have been created to help the emergency clinician work through the various types of angioedema. Patients with facial edema and concern for airway involvement require immediate stabilization. Following this, the clinician should assess for multisystem involvement, as this is more commonly seen in anaphylactic presentations.[21]

If no evidence of multisystem involvement is found, the patient should be assessed for urticaria or recent exposure to a known allergen, as this is generally seen in histamine-mediated angioedema. Histamine-mediated angioedema tends to develop more quickly, whereas bradykinin-mediated angioedema can develop progressively over several hours, continue for days, and will usually not have accompanied urticaria.[21]

Bradykinin-mediated angioedema is more probable in patients with a personal or family history of HAE and in those who are refractory to first-line therapy, such as antihistamines. In patients who present with a slower and more protracted course of facial swelling, the risk is higher for a bradykinin-mediated process.[21] Further delineation of the various subtypes of bradykinin-mediated angioedema might not be feasible in the emergent setting; however, a thorough history can be useful in cases such as ACEI-induced angioedema.

If swelling is localized to the gastrointestinal tract, typical symptoms may include severe abdominal pain, diarrhea, nausea, vomiting, and ascites. The presentation can appear severe enough to mimic an acute abdomen, which can lead to unnecessary imaging or surgical exploration. In cases where edema appears to be localized primarily to the gastrointestinal tract, a detailed history can be useful, especially in recurrent cases.

The differential diagnosis for facial and upper extremity swelling is very broad. **See Table 1**.

Table 1. Differential Diagnosis for Angioedema

- Histamine-mediated angioedema
- Bradykinin-mediated angioedema
  - Hereditary angioedema
  - Acquired angioedema
  - ACEI-induced
  - tPA- induced
- Idiopathic angioedema
- Urticaria
- Anaphylaxis
- Hydrostatic edema
- Oncotic edema
- Venous obstructive disease: superior vena cava syndrome, deep vein thrombosis
- Muckle-Wells syndrome[22]
- Gleich syndrome[23,24]
- Ascher syndrome[25]
- Melkersson-Rosenthal syndrome[26]
- NERDS syndrome[27]
- Dermatitis
- Cellulitis
- Filariasis

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; NERDS, nonerosive reflux disease; tPA, tissue plasminogen activator.

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Prehospital Care

Airway patency is the primary focus of prehospital management of angioedema. Local protocols must be followed if signs of airway compromise are present. Standard oxygenation techniques and cardiac monitoring should be initiated if head or neck involvement is apparent. Noninvasive ventilation (continuous positive airway pressure or bilevel positive airway pressure) should not be used, as the barotrauma may cause worsening angioedema. If there is concern for concurrent anaphylaxis, epinephrine should be given. If the patient's history is consistent with an immune-mediated or allergic cause, additional medications such as corticosteroids, antihistamines, epinephrine, and intravenous (IV) crystalloid fluids can be considered.

Emergency Department Evaluation

Initial Management and Stabilization

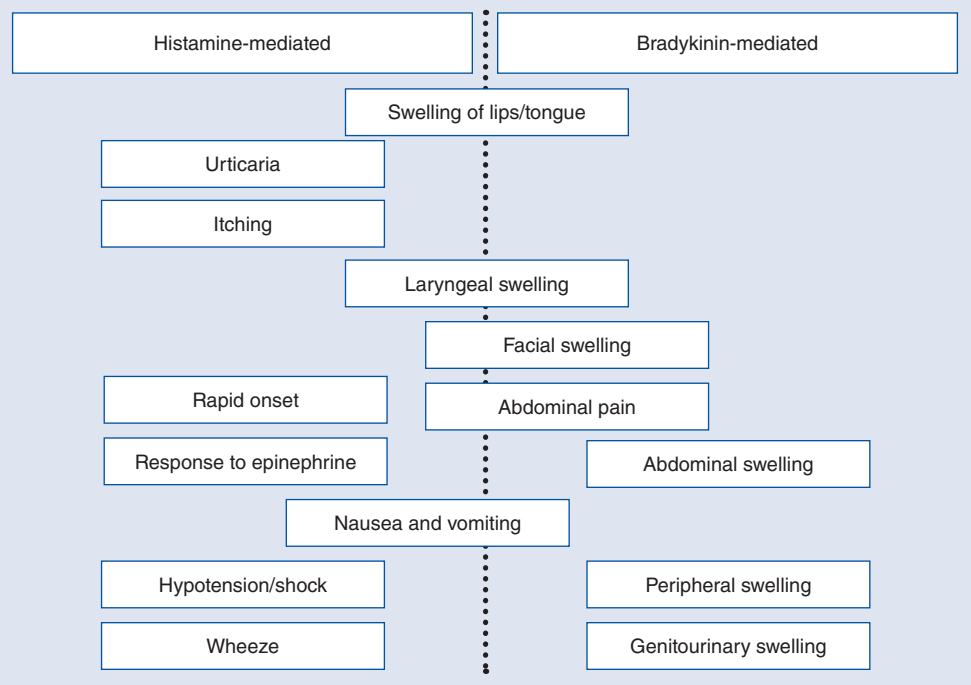
The initial management of angioedema includes obtaining a full set of vital signs along with immediate assessment of airway patency, presence of adequate breath sounds, and distal perfusion. The patient should be immediately placed on a monitor with continuous pulse oximetry and provided supplemental oxygen, if necessary. All patients will require frequent reassessments, as clinical conditions can change rapidly. The emergency clinician should have a low threshold to obtain a definitive airway if there are any signs of compromise.

History

The history should be directed at identifying potential causes, similar events in the past, and clinical progression of those prior episodes. The patient should be questioned about recent exposures (such as insect bites or stings), changes in diet, or any other unusual ingestions. The time of onset of symptoms will be helpful to guide the clinician on where the patient is in the timeline of the current episode and how aggressive their treatment should be. Histamine-mediated angioedema can occur quickly, often in under 1 hour, whereas HAE and AAE symptoms usually have a slower, progressive onset and frequently develop over several hours.[11] **(See Figure 2.)** Histamine-mediated angioedema will typically resolve within 24 to 37 hours, whereas untreated HAE and AAE will often have a more protracted course, typically lasting upwards of 48 to 72 hours, and occasionally lasting up to 5 days.[11]

A full review of any medications the patient might be taking should be performed, specifically asking about any supplements the patient may be using. While reviewing medications, particular attention should be given to NSAIDs, ACEIs or angiotensin receptor blockers (ARBs), estrogen-containing products, or any recent changes in dosage or route of

Figure 2. Distinguishing Histamine-Mediated Angioedema and Bradykinin-Mediated Angioedema



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International Journal of Emergency Medicine. Angioedema in the emergency department: a practical guide to differential diagnosis and management. Jonathan A. Bernstein, Paolo Cremonesi, Thomas K. Hoffman, John Hollingsworth. 2017. Volume 10, Issue 1, page 15.

administration.[28] To elicit whether there is a hereditary component to the angioedema, a full family history should also be obtained.

Physical Examination

The physical examination must be performed, repeated, and documented carefully, as the findings and the progression of symptoms will directly affect treatment and disposition of the patient. Following a brief, general examination, it is prudent to assess the patient's airway for signs of compromise. Findings that might indicate the presence of laryngeal edema include changes in phonation, hoarseness, stridor, inability to control secretions, or worsening dyspnea.[29] The role of adjuncts in the evaluation of the airway (eg, flexible laryngoscopy) is obvious when there is evidence of laryngeal compromise; however, in patients with facial edema but no signs of laryngeal involvement, the decision to perform flexible laryngoscopy should be made on a case-by-case basis.[30] **See Figure 3** for an example of a larygoscopic image of laryngeal edema.

Following an assessment of the patient's airway, breathing, and circulation, the next step will be to perform a more detailed examination of the patient, with special attention given to the gastrointestinal system, as well as inspection for cutaneous edema, urticaria, or rashes. **(See Figure 4 and Figure 5.)**

Figure 3. Laryngoscopic Image of Significant Edema of Aryepiglottic Folds

Laryngoscopic image showing significant edema of the aryepiglottic folds.

OTO Open. 2019. Volume 3, Issue 4. DOI: 10.1177/2473974X18805431. Adrian Williamson, Cory A. Vaughn, Ozlem E. Tulunay-Ugar. Angioedema involving the larynx after starting apixaban. Reprinted with permission from SAGE Journals.

While different causes of angioedema might have different symptoms, generally, most cases involve the face, extremities, and/or gastrointestinal tract. In some studies of HAE, the rates of gastrointestinal involvement might be as high as 73%, with abdominal pain being present in 95% of patients with gastrointestinal complaints.[31] The presence of urticaria will depend, in some part, on the underlying cause of the angioedema. Urticaria occurs secondary to degranulation of mast cells, which typically reside within the dermis layer of skin, causing localized vascular dila-

Figure 4. Lip and Tongue Swelling in Angioedema

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Figure 5. Urticaria

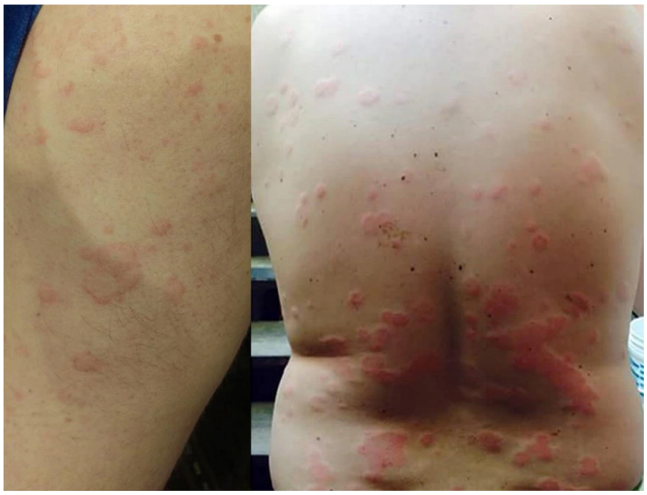

Image of urticaria, commonly seen in histamine-mediated angioedema. *Allergy, Asthma & Clinical Immunology*. Urticaria and angioedema. Amin Kanani, Stephen D. Betschel, Richard Warrington. 2018. Issue 14, Suppl 2:59. DOI: 10.1177/2473974X18805431 Reprinted by Creative Commons Attribution International License http://creativecommons.org/licenses/by/4.0/

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tion and edema.[11] As such, patients with histamine-mediated angioedema will present with urticaria while those with HAE, AAE, or ACEI-induced angioedema might not present with urticaria.[11]

Diagnostic Studies

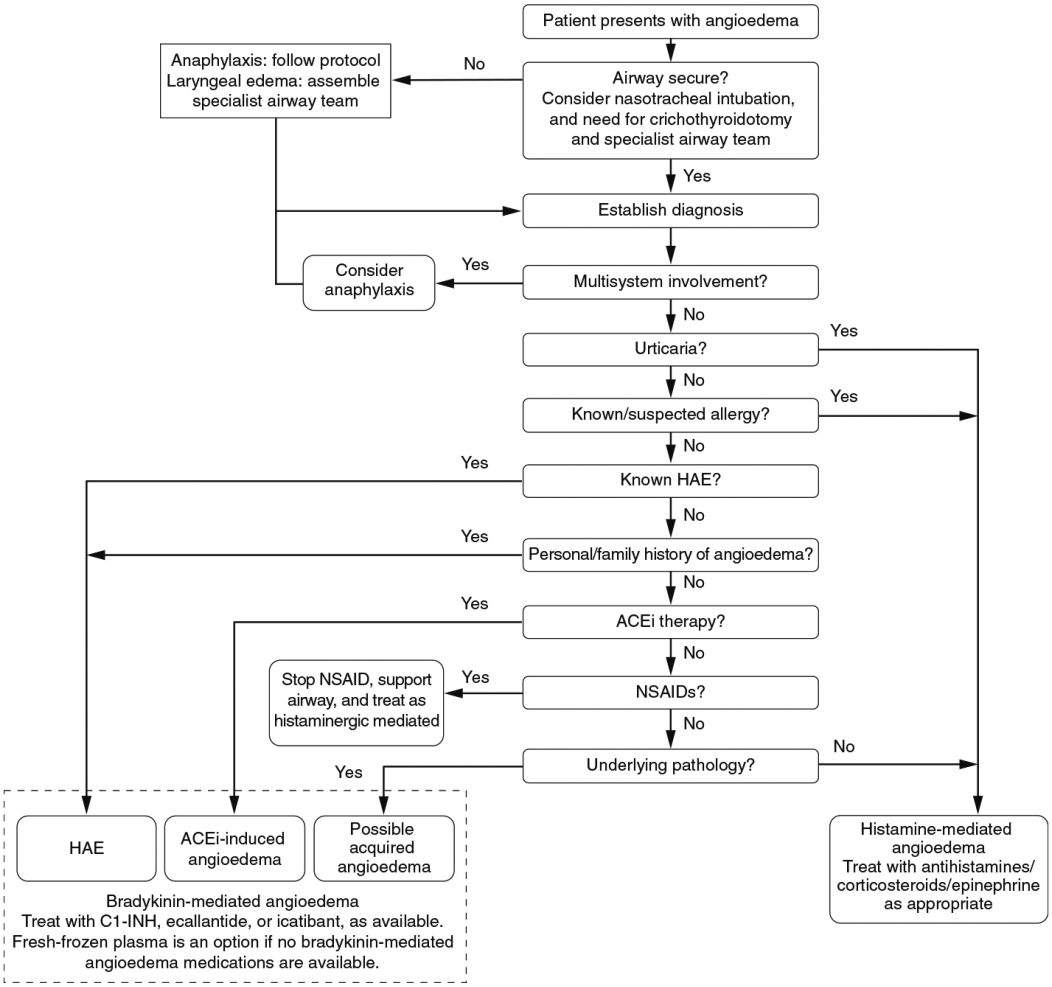
Diagnosing the exact cause of angioedema is usually outside of emergency practice and is more commonly performed in the outpatient setting. Most of the laboratory tests needed to diagnose the specific forms of angioedema require several days to weeks to result. While there is no rapid, point-of-care diagnostic test available, there is a general framework the emergency clinician can use to help guide in preliminarily diagnosing the patient.[11] **(See Figure 6.)**

Laboratory Studies

There are several different etiologies for angioedema; however, only a few have reliable laboratory changes that are useful in diagnosis. HAE can be diagnosed by measuring C1-INH concentrations and function. In patients with a strong family history of HAE or in those who have a sufficiently convincing personal history, it is appropriate to obtain a C4 concentration level in the ED as a screening tool, since low levels of C4 are normally found during the immediate period surrounding an attack.[32] As seen in **Table 2 (page 9)**, low levels of C4 can help guide further testing, such as C1-INH concentration and function, which helps differentiate between HAE type 1 and HAE type 2. Of note, there have been case reports of patients with HAE who had consistently normal C4 concentrations, which has led some to consider implementing a C4c/C4 ratio as the superior diagnostic screening test.[33,34] However, serum C4 concentration still appears to be the more widely used screening test.

In patients with low C4 concentrations or elevated C4c/C4 ratio, the next step is assessing the concentration and function of C1-INH. Low concentrations of C1-

Figure 6. Flow Diagram for Diagnosis of Angioedema in the Emergency Department



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INH are suggestive of HAE type 1, whereas low function of C1-INH is more suggestive of HAE type 2. HAE with normal C1-INH (previously known as HAE type 3) is a rare form of HAE with normal serum complement levels that has been linked to genetic mutations in factor XII, angiopoietin-1, and plasminogen gene.[35]

Both HAE and AAE have similar laboratory findings of low C4 and low C1-INH concentration or function, and further testing is required to differentiate them correctly. While family history of the disease can point to HAE, up to 25% of unrelated HAE cases are secondary to a de novo mutation, which calls for definitive testing.[36] Serum C1q protein concentration can therefore be used to differentiate HAE from AAE, as C1q protein is normal in HAE and low in AAE.[35-37] Other testing, such as anti-C1-INH autoantibodies, can be used to further describe the subtype of AAE.

Unlike HAE, in which testing of C1-INH, C4, and other complement levels aid in diagnosis, there is no routine laboratory test to help diagnose ACEI-induced angioedema.[37] The diagnosis therefore relies on clinical presentation and history of concurrent ACEI use. While some studies have examined the utility of measuring serum C-reactive protein levels in ACEI-induced angioedema, this has still not been widely adopted.[38]

Serum tryptase and histamine concentrations have been used to retrospectively diagnose anaphylaxis and histamine-mediated angioedema; however, serum histamine and tryptase levels are not always elevated, even in patients with severe symptoms.[39] Other biomarkers of interest include platelet-activating factor or carboxypeptidase A3; however, these have not yet been developed for clinical use.[39,40]

Given that most causes of angioedema occur either secondary to histamine release from mast cell degranulation or because of a bradykinin-mediated process, there appears to be little role for the routine testing of eosinophils in most common causes of angioedema. An exceptionally rare form of angioedema called Gleich syndrome (episodic angioedema associated with eosinophilia) has been described; however, given the paucity of robust literature, there is currently no well-established guideline for monitoring eosinophil counts.

Imaging Studies

Additional diagnostic tests, such as computed tomography (CT) imaging, are frequently obtained in patients with concerning abdominal pain. In patients with abdominal pain secondary to an acute angioedema attack, the most common radiographic sign is ascites. Other findings are segmental bowel wall edema with or without skip segments and straightening of bowel segments.[41]

Treatment

Airway Management

The treatment of angioedema begins with a thorough consideration of airway management. There should be a low threshold for the establishment of a definitive airway. It is recommended that the airway be secured early if there is concern for airway compromise or a reasonable potential for imminent compromise. Given the nature of angioedema, intubation will likely be technically challenging, as anatomy can become distorted. Clinicians should avoid over-manipulation of the airway, as minor trauma can worsen edema. When the decision is made to secure an airway, emergency clinicians should optimize their chance of success by maximizing the safe apnea time and considering which backups and adjuncts to have available in the room. Of note, according to papers by Ishoo et al[42] and Das et al,[43] patients with edema localized to the lips alone do not have an increased risk for requiring intubation.

Supplemental oxygen should be given to all patients with angioedema prior to intubation; however, care should be taken to avoid positive pressure, given the concern for worsening edema in the setting of barotrauma. In cases where there is marked lingual

Table 2. Differential Diagnosis of Angioedema According to Laboratory Results

Type of Angioedema	C1-INH Antigenic Level	C1-INH Functional Level	C4 Level	C1-q Level
HAE-1	Low	Low	Low	Normal
HAE-2	Normal	Low	Low	Normal
HAE with normal C1-INH	Normal	Normal	Normal	Normal
ACID	Low	Low	Low	Low
Angioedema due to ACEI	Normal	Normal	Normal	Normal
Nonclassified angioedema[a]	Normal	Normal	Normal	Normal

[a]Nonclassified implies that no cause has been identified.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACID, acquired angioedema due to C1-INH deficiency; C1-INH, C1 esterase inhibitor; HAE-1, hereditary angioedema type I (due to C1-INH deficiency); HAE-2, hereditary angioedema type 2 (due to C1-INH defect).

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swelling without significant laryngeal edema, nasotracheal intubation with fiberoptic visualization might be useful, as this approach will bypass the tongue, and can often be performed without paralytics or sedation if adequate local anesthesia is obtained with atomized/nebulized/topical lidocaine. We do not recommend paralyzing a patient with angioedema until a clear view of airway anatomy can be obtained. We also suggest preloading the fiberoptic scope with an endotracheal tube, so if there is significant edema present, intubation can be performed immediately.

When approaching a patient with a potentially difficult airway, it is recommended to have a surgical airway set up in the room as part of a dual-setup approach. Recent data from a prospective multicenter cohort study show that, of 19,071 patient encounters that resulted in intubation, angioedema was found to be the cause in 98 (0.5%). First-attempt success was achieved in 81%, with emergency physicians performing the procedure in 94% of encounters. The most common device used was a flexible endoscope (49%), and 42% of attempts were performed via a nasal route. Nasotracheal first attempts were observed to have higher success than orotracheal routes (95% vs 70%, respectively). Sedation with paralysis was performed in 61% of cases, whereas topical anesthesia with or without sedation occurred in 26% of cases. A cricothyrotomy was performed in 2% of patients. There were no deaths observed in the study.[40]

Pharmacologic Treatment

The management of angioedema has 3 distinct phases: (1) management of the acute episode, (2) short-term prophylaxis, and (3) long-term prophylaxis. In the ED, management is focused primarily on acute episodes and occasionally short-term prophylaxis. If the suspected etiology is medication- or allergic-induced, the trigger must be removed. Given that most cases of angioedema are histaminergic in origin, treatment has historically been centered on managing this aspect of the disease.[41] Nonetheless, particularly in bradykinin-mediated angioedema, reliance on pharmacologic tools should not take precedence over careful airway management.

In histamine-mediated forms of angioedema, standard therapy for anaphylaxis consisting of epinephrine, corticosteroids, antihistamines, and IV crystalloid fluids is recommended. If there is suspicion for anaphylaxis or if the exact underlying cause of the angioedema is unknown, histamine-mediated angioedema should be assumed.[3]

For more information on management of allergic reactions and anaphylaxis, see the July 2022 issue of *Emergency Medicine Practice*, "Management of Allergic Reactions and Anaphylaxis in the ED" at www.ebmedicine.net/Anaphylaxis

Pharmacologic Treatment for Histamine-Mediated Angioedema

Epinephrine

Epinephrine is a potent nonselective alpha and beta agonist. Its action on alpha-1 receptors results in vasoconstriction and subsequent decrease in mucosal edema. Beta-1 agonism leads to improved cardiac contractility, while its effect on beta-2 receptors leads to bronchial smooth muscle relaxation, causing bronchodilation. Epinephrine remains the first-line therapy in the management of anaphylaxis and should be given via the intramuscular (IM) route into the anterolateral aspect of the thigh. It should be administered without delay, with an initial dose 0.3 to 0.5 mL (0.3–0.5 mg) of the 1 mg/mL concentration, which can be repeated every 5 to 20 minutes, up to 3 doses.[3,44,45] The dose for children (<30 kg) is 0.01 mg/kg (maximum 0.3 mg) of the 1mg/mL concentration.[46]

IV epinephrine is not a first-line therapy and should be considered only in patients requiring multiple doses of IM epinephrine and should begin at doses of 1 to 4 mcg/min (0.01-0.02 mcg/kg/min).[3] The use of IV epinephrine in patients presenting with refractory shock in the setting of angioedema is supported by a clinical review by Johnston et al.[47] A "dirty" epinephrine drip can be created quickly by injecting 1 mg of epinephrine (crash-dose epinephrine) into 1 L of normal saline. This results in a final concentration of 1 mcg/mL, which can be administered wide-open through an 18-gauge IV, providing 20 to 30 mL/min (20-30 mcg/min) of epinephrine.[3] Administration of epinephrine through other routes (eg, subcutaneous injection or inhalation from a metered-dose inhaler or nebulizer, or given in muscles other than the anterolateral thigh) is not recommended for the treatment of anaphylaxis because it is more difficult to rapidly achieve high plasma and tissue concentrations.[41,44]

Patients who are on concurrent beta-blocker therapy, or those who continue to have refractory hypotension following adequate dosing of epinephrine may be given glucagon 1 to 5 mg IV every 5 minutes. The proposed mechanism of action for glucagon is that it may alleviate hypotension by increasing cyclic adenosine monophosphate independent of the adrenergic receptors, although this remains unproven.[3]

Antihistamines

Antihistamines have a slower onset of action and should be used as adjuncts to epinephrine. Diphenhydramine is a first-generation H1 antagonist that can be used in doses of 25 to 50 mg IV in adults to relieve the cutaneous symptoms, such as urticaria and itching, in combination with a second-generation antihistamine agent (eg, cetirizine, loratadine, fexofenadine, levocetirizine, desloratadine). However, the administration of second-generation antihistamines might not

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be feasible in certain patients who are intolerant of an oral formulation.[3] The pediatric dosage of diphenhydramine is 1 mg/kg IV, with a maximum dose of 50 mg.[41] While unlikely to be helpful in bradykinin-mediated angioedema, their overall favorable side-effect profile means they can be provided in the absence of a clear history of HAE or ACEI-induced angioedema.[48] The addition of an H2 receptor antagonist can be considered to prevent hypotension and urticaria associated with pruritus secondary to histamine release. While unlikely to be harmful if given, there are no large validated studies to support the use of H2 receptor antagonists for allergic emergencies associated with angioedema in the acute setting.[5]

Corticosteroids

Corticosteroids are another adjunct commonly used in the management of angioedema. This class of medication should not be used as monotherapy in the management of anaphylaxis or histamine-mediated angioedema without anaphylaxis, as the mechanism of action of corticosteroids requires the activation and inhibition of a variety of proteins and peptides, leading to a delayed effect. This class of medication is considered to be an integral component of the management of asthma; however, corticosteroids have not yet been shown in large randomized controlled trials to be effective in the management of histamine-mediated angioedema with or without anaphylaxis.[45,49] With that said, it is still a commonly trialed medication in the emergency setting, and a dosage of methylprednisolone 125 mg IV has been suggested in a systematic review and by a consensus panel.[3,5] Given their extensive side-effect profile, the emergency clinician should consider weighing the potential benefits of improved urticaria and possible improvement of angioedema with the effects of hyperglycemia, hypertension, and infection.

Pharmacologic Treatment for Bradykinin-Mediated Angioedema

Typically, C1 inhibitors, bradykinin B2 receptor antagonists, and kallikrein inhibitors are used for treatment of bradykinin-mediated angioedema. Typical doses are shown in **Table 3**.

C1 Esterase Inhibitor Replacement Therapy

C1-INH replacement therapy has become a mainstay in the management of acute attacks of bradykinin-mediated angioedema. The proposed mechanism of action is downregulation of prekallikrein to kallikrein. Deficiency in C1-INH leads to an increase in kallikrein and hence to increased production of bradykinin, which itself is a potent vasodilator, leading to localized angioedema. Restoring C1-INH inhibits further production of bradykinin, thus allowing a reduction in

Table 3. Drugs Used for Management of Bradykinin-Mediated Angioedema[50]

Drug	EMA and FDA Indications	Recommended Dosage	Mechanism	Potential Adverse Effects
Berinert® (plasma-derived C1-INH)	Acute attacks	20 units/kg IV	Deficiency replacement	Theoretical: transmission of infectious agent; headache, injection site reaction, rash, pruritus, antibody development, hypersensitivity reaction
Cinryze® (plasma-derived C1-INH)	Long-term prophylaxis	1000 units IV every 3-4 days		
	Short-term prophylaxis (off-label)	1000 units IV		
Haegarda® (plasma-derived C1-INH)	Long-term prophylaxis	60 units/kg IV every 3-4 days		
Ruconest® (recombinant C1-INH)	Acute attacks	<84 kg: 50 units/kg IV (max 4200 units) ≥84 kg: 4200 units IV		Contraindicated in rabbit-sensitized individuals; antibody development, headache, hypersensitivity
	Prophylaxis (off-label)	<84 kg: 50 units/kg IV twice weekly (max 4200 units/dose) ≥84 kg: 4200 units IV twice weekly		
Ecallantide	Acute attacks	30 mg subQ (administered as 3 injections of 10 mg/mL each); may repeat x1 in 24 hours if attack persists	Inhibits plasma kallikrein	Headache, nausea, antidrug antibodies, injection-site reactions, risk for anaphylaxis
Icatibant	Acute attacks	30 mg subQ; may repeat every 6 hours if response is inadequate (max 90 mg/day)	Bradykinin 2 receptor antagonist	Injection-site reactions, antibody development, increased serum transaminase

Abbreviations: C1-INH, C1 esterase inhibitor; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; IV, intravenous; SubQ, subcutaneous.

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edema and associated symptoms. There are 4 United States Food and Drug Administration (FDA)-approved formulations of C1-INH concentration available in the United States. Three of those, Berinert®, Cinryze®, and Haegarda® are produced from pooled human plasma, whereas the fourth, Ruconest®, is a recombinant form of human C1-INH.

Berinert® and Cinryze®

Berinert® is a C1-INH formed from pooled plasma. It should be warmed to room temperature before administration and is given via IV push at 4 mL/min. The FDA approved this medication in 2009 for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients at a dose of 20 units/kg IV.[51] This approval came about following the IMPACT-2 trial, which was an open-label, uncontrolled, multicenter extension of the IMPACT-1 trial. IMPACT-1 was a placebo-controlled prospective trial that showed effectiveness of Berinert® in treating acute abdominal and facial HAE attacks.[52] The IMPACT-2 trial demonstrated that, in 1085 attacks from 57 patients, the median time to onset of symptom relief was 0.46 hours, with complete resolution of symptoms in 15.5 hours. The IMPACT-2 trial found no inhibitory antibodies in any of the patients in the trial and found no relevant differences in serious adverse events between patients with and without anti-C1-INH antibodies, demonstrating that this medication is likely to remain efficacious over the long term. The IMPACT-2 trial was performed with participants receiving a single dose of 20 units/kg given intravenously, and found this dosage led to symptom resolution in 99% of HAE attacks.[52]

Cinryze® is another C1-INH formed from pooled plasma that has become available since 2008. A double-blind placebo-controlled trial performed by Zuraw, et al of 68 subjects (35 in the C1-INH group and 33 in the placebo group) demonstrated an estimated median time to onset of unequivocal relief was statistically significantly at 2 hours for the C1-INH group versus more than 4 hours for placebo. It also demonstrated that 60% of patients had onset of unequivocal relief by 4 hours compared with 42% in the placebo group, although this was not statistically significant. When comparing the median time to complete resolution of symptoms, the study group had a statistically significant reduction in time of 12.3 hours compared to 25.0 hours in the placebo group.[53]

A second study was performed by Zuraw et al where 24 of the 71 subjects randomly assigned to a study group in the acute-attack treatment trial were also enrolled in a prophylactic efficacy trial.[53] The results of this trial demonstrated an estimated average difference in attack rates of 6.47, with no evidence of significant sequence or period effect between subjects receiving C1-INH and those receiving placebo.[53]

Following these 2 trials, 88 patients were enrolled in an open-label extension study for the treatment of acute attacks. Findings from this study demonstrated the median time to a response was 30 minutes, irrespective of whether a subject was given open-label treatment fewer than 4 times, 4 to 9 times, or 10 times or more.[53]

While Cinryze® is FDA-approved for routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (aged ≥6 years) with HAE, it is not approved for the management of acute attacks. The dosage for adults and children aged ≥2 years is 1000 units IV every 3 to 4 days; for children aged 6 to 11 years, the dosage is 500 units IV every 3 to 4 days.[54]

Recombinant C1 Esterase Inhibitor

Recombinant human C1-INH (rhC1-INH) (Ruconest®) contains an amino acid sequence identical to that of human C1-INH and is therefore able to serve as an analogue. It is unique in that it is created from the milk of transgenic rabbits rather than derived from human plasma donors, which can potentially relieve the concern for infectious transmission.[55]

Zuraw et al conducted 2 independent randomized saline-controlled double-blind studies to evaluate the efficacy and clinical safety of rhC1-INH in the treatment of acute angioedema attacks in patients with known HAE.[56] One trial, referred to as the "North American" trial was conducted in 26 United States and 4 Canadian centers. The other trial, referred to as the "European" trial, was conducted in 11 centers in Italy, Spain, Romania, the United Kingdom, and Israel. [56] Patients with an eligible attack were randomized equally (1:1:1) to receive IV 100 or 50 units/kg rhC1-INH or saline in the North American study, or (1:1) to receive 100 units/kg rhC1-INH or saline in the European study. Both the North American study and the European study were closed after interim analyses, due to compelling statistically significant positive efficacy findings and no apparent adverse safety findings. Treatment with rhC1-INH 100 units/kg (n=29) and 50 units/kg (n=12) achieved the primary endpoint with a median significant reduction in time to beginning of relief of symptoms of 66 minutes (95% confidence interval [CI], 61-122) and 122 minutes (CI, 72-136), respectively, compared with saline (n=29), at 495 minutes (CI, 245-520), $P < .001$ and $P = .013$.[56]

In 2014, rhC1-INH received FDA approval for treatment of acute attacks in adult and adolescent patients with HAE. The recommended dose for rhC1-INH is 50 units/kg IV for patients weighing <84 kg and 4200 units IV for those weighing ≥84 kg.[57]

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Non–C1 Esterase Inhibitor Concentrate Therapy

Icatibant

Icatibant (trade name, Firazyr®), is a synthetic peptide that is structurally similar to bradykinin, allowing the peptide to function as a specific inhibitor of the bradykinin B2 receptor. Icatibant was compared to placebo in 2 clinical trials (FAST-1[58] and FAST-3[59]), in which the results were discordant with each other. In FAST-1, icatibant did not demonstrate a statistically significant improvement in median time to clinically significant relief, whereas patients enrolled in the FAST-3 trial did demonstrate a statistically significant improvement in median time to clinically significant relief (at least 50% reduction in symptoms). In the FAST-2 trial, icatibant was shown to have a shorter time to clinically significant relief of symptoms when compared with tranexamic acid.[60] Based on these results, icatibant was given FDA approval in 2011 for treatment of acute attacks of HAE in adults aged ≥18 years.[61] Icatibant is given at a dosage of 30 mg injected subcutaneously in the abdominal area, and can be re-dosed in 6-hour intervals for a maximum of 3 doses in a 24-hour period.[61]

Icatibant has been studied in ACEI-induced angioedema.[62] When compared to a corticosteroid and antihistamine combination therapy in ACEI-induced angioedema, icatibant was found to have a shorter median time to complete resolution of ACEI-induced angioedema (8 hours vs 27.1 hours). There was no reported recurrence of angioedema in this prospective trial.[63]

Ecallantide

Ecallantide is a 60-amino-acid polypeptide derived from *Pichia pastoris* yeast cells that functions as a specific reversible inhibitor of plasma kallikrein. Kallikrein cleaves high-molecular-weight kininogen into bradykinin which, in turn, cleaves factor XII, ultimately producing fXIIa. This forms a strong positive feedback loop, amplifying the effects of bradykinin, leading to angioedema. Bradykinin binds to transmembrane, G protein-coupled receptors, B1 and B2. The B2 receptor is constitutively expressed and is responsible for mediating most of the kinins' vascular and metabolic actions.[62]

Clinical efficacy of ecallantide for treatment of acute HAE was first established in the EDEMA trials with 3 Phase 2 trials and 2 Phase 3 trials.[64,65] The EDEMA2 trial, which was a dose-ranging study, was influential in establishing the optimal dose and administration of ecallantide.[64] The EDEMA3 trial was a randomized, double-blind, placebo-controlled trial in which patients with known HAE received either placebo or 30 mg of subcutaneous ecallantide.[65] Results from the EDEMA3 trial demonstrated a statistically significant difference in patient-reported treatment outcome score (to assess improvement in symptoms and change from baseline in symptom complex severity score).[65] The EDEMA4 trial also showed a significant reduction in mean complex severity score at 4 hours for ecallantide versus placebo.[66]

In 2009, ecallantide was given FDA approval for use in patients aged ≥16 years with acute attacks of HAE; in 2014, the FDA expanded its use to patients aged ≥12 years. The recommended dosage is 30 mg, administered as 3 subcutaneous doses of 10 mg each. The doses are given away from the site of angioedema at 3 separate sites, at least 2.5 inches apart, in the abdomen, upper arm, or thigh.[67] This medication carries an approximately 4% risk for anaphylaxis, and as such is not recommended for self-treatment by patients at home.[67] There are 2 case reports that suggest ecallantide may also be effective in the management of non-histaminergic, idiopathic angioedema; however, the data are too limited to make recommendations for its use in this patient population.[62]

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is a second-line therapy in the acute treatment of angioedema attacks and should be used only if the first-line therapies discussed previously are not available. To date, there are no studies comparing FFP directly with first-line therapies such as C1-INH agents, icatibant, or ecallantide. There have been case reports that have demonstrated mixed effectiveness in its use in acute attacks of HAE or ACEI-induced angioedema.[35,37,68-70] One retrospective cohort study of 20 patients found FFP reduced the risk for intubation in non-HAE patients.[71] Given that a unit of FFP is typically between 200 and 250 mL and the usual dose is 2 to 4 units, there is a possibility of fluid overload, which will often limit its feasibility as a treatment modality, especially in patients who are already clinically volume-overloaded on presentation to the ED. While FFP does contain C1-INH (among other substances), it is in a diluted form compared to recombinant or plasma-derived C1-INHs. Concerningly, it has been suggested that since FFP contains substrates such as high-molecular-weight-kininogen, there could be a paradoxical worsening of angioedema; however, there is little evidence to support this theory.[72] Other concerns with FFP are hypersensitivity reactions and its potential for infectious transmission.

Prophylactic Medications

There are several classes of prophylactic medications that have been used in the management of angioedema. Androgens such as danazol, stanozolol, and oxandrolone, have been used as prophylaxis against AAE.[73] Antifibrinolytics, such as tranexamic acid and aminocaproic acid have also been used in managing ACEI-induced angioedema in the past.[74] In 2018, a monoclonal antibody and kallikrein inhibitor, lanadelumab, received FDA approval for prophylaxis

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to prevent attacks of HAE in patients aged ≥12 years.

In 2020, Haegarda® a subcutaneous form of plasma-derived C1-INH, received FDA approval for routine prophylaxis to prevent HAE attacks in adolescent and adult patients. While these new treatments are dramatically changing the outpatient management of angioedema, their use in the ED is limited.

Special Populations

Pediatric Patients

While there has not been a robust body of literature published on special populations with bradykinin-mediated angioedema, a few smaller studies have begun to raise some important considerations. HAE can be a difficult disease to manage in the ED, as definitive diagnosis often requires outpatient testing, and management of the disease involves expensive medications that might not be available in some EDs.

This difficulty is compounded when managing the pediatric population. It is estimated that between 50% and 75% of patients with HAE will have their first attack by the age of 12.[75] It is further thought that the mean age of onset is between 5 and 11 years of age.[76] Given that many patients with HAE will have symptoms early in childhood, it is imperative that emergency clinicians be aware of the differences in the management of children. When compared with adults, laryngeal edema in the pediatric population can lead to asphyxia relatively sooner due to a smaller airway diameter. In addition, fiberoptic laryngoscopy in the pediatric patient is more technically difficult, due to lower rates of patient compliance.[77]

In a retrospective observational study of 83 ED visits from 16 patients, García Sánchez et al found that, among the group of pediatric patients with suspected acute attacks of angioedema in the ED, 43.7% presented due to respiratory distress. Of this subgroup of patients, 16.1% were considered true acute attacks of angioedema, with the remaining cases attributed to bronchospasm, pneumonia, or upper respiratory tract infections. Another 33.8% presented due to abdominal symptoms, of which, roughly 45% were attributed to an acute attack.[78]

In the pediatric population, abdominal involvement is often associated with a colicky abdominal pain that can mimic an acute abdomen. This can lead to unnecessary surgical intervention and prolonged hospital courses. The differential diagnosis for abdominal pain in pediatric patients is extensive, and includes acute appendicitis, mesenteric lymphadenitis, intussusception, and perforated viscus from any etiology.[78] In patients with recurrent colicky abdominal pain, an abdominal ultrasound is recommended, as certain pathologies such as intussusception (which has been associated with HAE) and bowel wall edema can be reliably seen using this radiation-sparing imaging modality.[78]

Although most HAE consensus guidelines recommend C1-INH replacement therapy as the preferred option for on-demand treatment, short-term prophylaxis, and long-term prophylaxis in pediatric patients, there are only a few robust studies that support these recommendations.[79,80] FDA approval was given to both plasma-derived C1-INH concentrate therapies, Berinert® and Cinryze®, for the management of HAE in the pediatric population. In 2014, the FDA granted approval for rhC1-INH (Ruconest®) for the management of acute HAE attacks in both adults and adolescents. There are limited data examining the safety and efficacy of ecallantide in patients aged <12 years.

Pregnant and Lactating Patients

Pregnant and lactating patients require special consideration when managing bradykinin-mediated angioedema.[81] While incompletely understood, the physiologic changes in pregnancy can mitigate, aggravate, or have no effect on the patient's underlying HAE.[82] Such varied responses during pregnancy makes managing HAE more difficult. Though poorly studied, the preferred acute treatment for HAE attacks remains the plasma-derived C1-INH, Berinert®, given IV at 20 units/kg.[83]

rhC1-INH (Ruconest®) is recommended for use during pregnancy or breast-feeding if plasma-derived C1-INH is not available and there are no obvious contraindications.[83] Similarly, icatibant may be used in the case of life-threatening attacks during pregnancy when plasma-derived C1-INH is not available or has not been efficacious for a particular patient. Recent small studies have shown rhC1-INH and icatibant to be safe in pregnancy.[82]

Controversies and Cutting Edge

Tranexamic acid has been suggested as a therapeutic option for treatment of HAE as well as ACEI-induced angioedema. Tranexamic acid is an antifibrinolytic agent that inhibits conversion of plasminogen to plasmin, a key step in kallikrein activation and bradykinin formation. A 2018 systemic review evaluated 31 studies and found that there is no strong evidence that supports the use of tranexamic acid for acute angioedema management.[84] One randomized controlled trial found the median time to relief of symptoms was 2 hours for icatibant and 12 hours for tranexamic acid ($P < 0.001$).[85] A 2021 case report showed improved ACEI-related angioedema symptoms after tranexamic acid use, but concomitant use of histamine-directed medications could have contributed to observed result.[74] Tranexamic acid may be better when compared to no therapy, but if possible, other options should be utilized.[85,86]

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Disposition

Staging and Treatment Location

The disposition of patients with angioedema will invariably be determined by the degree of concern for airway involvement. While there remains a paucity of data surrounding high-quality validated guidelines for the disposition of patients with angioedema, several smaller studies have attempted to risk-stratify patients based on various criteria.

Ishoo et al performed a single-center retrospective chart review of 80 patients with 93 episodes of angioedema over an 11-year period who presented to the ED for treatment. The study found that voice change, hoarseness, dyspnea, and rash were significantly correlated with need for intensive care unit (ICU) admission, whereas voice change, hoarseness, dyspnea, and stridor were present in patients requiring airway intervention.[42] The patients in the study were categorized based on the anatomic location of the angioedema as listed in **Table 4**. Disposition and intervention based on staging are described in **Table 5**. However, this study was limited, in that the data were derived from a retrospective analysis from a single institution from 1985-1995. Since this paper has been published, there have been significant advancements in the management of angioedema and, more specifically, bradykinin-mediated angioedema.

In 2021, a retrospective chart review was published that evaluated a staging system based on angioedema localization as a method of predicting need for admission or airway intervention.[43] This staging system, a modified form of the Ishoo stages, is outlined in **Table 6**. In this system, patients in Stage 4 were more likely to require ICU care without airway intervention (probability 17%) and with airway intervention (67%) compared with patients in stage 1 without airway intervention (2.5%) and with airway intervention (0.1%). Conversely, patients in stage 1 were more likely to be treated in the ED and discharged (85%) compared with stage 4 (0%). Additional results of the study are listed in **Table 7, page 16**.

General Disposition Recommendations

For all cases of angioedema, it is imperative to offer discharged patients strict return precautions if their symptoms worsen or if they begin to develop airway compromise,[5] in addition to recommedation for prompt primary care provider follow-up. If there is concern for an allergic or immunologic component to the patient's angioedema, treatment with a short course of corticosteroids and antihistamines is reasonable. It is also recommended to discharge these patients with an epinephrine autoinjector.

Patients with previously diagnosed HAE can be discharged from the ED with targeted therapy to reduce the risk for recurrence.

Patients with ACEI-induced angioedema should be advised to discontinue their ACEIs, avoid taking this class of medications in the future, and consult with their primary care provider for suitable alternative medications.

Table 4. Ishoo Staging, by Anatomic Location

Stage	Site	Episodes (%)
I	Facial rash, facial edema, lip edema	31
II	Soft palate edema	5
III	Tongue edema	32
IV	Laryngeal edema	31

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Table 6. Angioedema Staging, by Localization

Stage	Site
1	Lip, face, periorbital, extremities, total body/diffuse swelling
2	Soft palate, posterior pharynx
3	Tongue
4	Larynx

Adapted from *Acute Medicine & Surgery.* Volume 8, Issue 1. Conor Dass, Maggie Mahaffa, Elizabeth Dang, et al. Evaluation of staging criteria for disposition and airway intervention in emergency department angioedema patients. © 2021 The Authors. *Acute Medicine & Surgery* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Association for Acute Medicine.

Table 5. Treatment Location and Intervention Based on Ishoo Staging

Stage	Outpatient (%)	Floor Admittance (%)	ICU Admittance (%)	Intervention (%)	*P*
I	48	52	0	0	0.001
II	60	40	0	0	0.001
III	26	7	67	7	0.001
IV	0	0	100	24	0.012

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Case Conclusions

CASE 1

For the 23-year-old man who presented by EMS with abdominal pain…

You had a wide differential for this patient with recurrent abdominal pain, including appendicitis, testicular torsion, mesenteric ischemia, intussusception, small-bowel obstruction, sexually transmitted infections, pyelonephritis, liver disease, and gastroparesis, among others. You found the recurrent nature of his symptoms, coupled with a family history of what appeared to be angioedema interesting. You noted that, in spite of previous negative workups, his presentation was concerning for acute emergent pathology, so you obtained repeat laboratory tests and ordered a CT of his abdomen and pelvis with IV contrast, in which you noted a leukocytosis and bowel wall edema without ischemia. His examination was concerning, so you consulted surgery, and they recommended observation to medicine and further diagnostic evaluation. You remembered that HAE can present with bowel edema, so you added on complement and C1-INH levels and admitted him to the hospital. Upon chart review, you noted the patient had low C1-INH levels and was currently being treated with C1-INH, with improved symptoms.

CASE 2

For the 48-year-old woman who presented with lip swelling…

Your differential for acute lip swelling included allergic reaction, anaphylaxis, soft-tissue infection including abscess, as well as angioedema from the patient's ACEI use. Your examination was not consistent with infectious etiology, and you realized that labs and imaging wouldn't be useful for the other potential causes of this patient's lip swelling. Given that the patient had no history of allergic reactions in the past and no obvious allergic trigger, you decided that her ACEI use was most likely responsible for her symptoms. You knew that ACEI-induced angioedema is managed with medication cessation and observation, so you watched the patient in the ED for 6 hours. She had no progression of symptoms or signs of airway compromise, so you discharged her with strict return precautions and instructions to stop taking her ACEI medication and to speak with her primary care physician about changing to another antihypertensive drug. You called the patient the next day and she reported that her symptoms had improved significantly.

Summary

Angioedema is a physical manifestation of a variety of disease processes. It results from mast cell degranulation or excessive bradykinin formation caused by allergic or immunologic reactions, medications (such as ACEIs and NSAIDs), or a genetic and/or functional deficiency of C1-INH. Emergency clinicians must understand the various etiologies of angioedema in order to effectively target therapy.

Initial management involves assessment of the patient's airway, and stabilization if the patient is exhibiting signs of airway compromise, particularly in pediatric patients. After determining the most likely cause of angioedema, targeted therapeutic options can be utilized, such as epinephrine, antihistamines, C1-INH, rhC1-INH, inhibitors of kallikrein, or bradykinin B2 receptor blockers, and corticosteroids.

Table 7. Number and Predictive Probabilities of Disposition and Airway Intervention, Based on Stage

Stage	Treated in ED and Discharged		Non-ICU Admit		ICU (any)		ICU (Without Airway Intervention)		ICU (With Airway Intervention)	
	n (%)	PP	n (%)	PP	n (%)	PP	n (%)	PP	n (%)	PP
1	160 (73)	0.85	24 (46.2	0.13	4 (8.2)	0.02	4 (13.8)	0.025	0	0.001
2	13 (5.9)	0.52	7 (13.5)	0.28	5 (10.2)	0.2	5 (17.2)	0.086	0	0.086
3	46 (21)	0.45	21 (40.4)	0.2	36 (73.5)	0.35	18 (62.1)	0.21	18 (90)	0.16
4	0	0	0	0	4 (8.2)	1.0	2 (6.9)	0.17	2 (10)	0.67

Abbreviations: ED, emergency department; ICU, intensive care unit; PP, predictive probability.

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Risk Management Pitfalls in Managing Angioedema in the Emergency Department

1. **"I thought all angioedema cases are a form of allergic reaction and should be treated as such."** While 40% to 70% of angioedema presentations are histamine-mediated, it is important to recognize other potential causes such as medications (ACEI, tPA, NSAIDs) as well as HAE and AAE, which are related to excess bradykinin and will not respond to typical therapies used for allergic reactions.

2. **"The patient had only mild lip swelling with no other symptoms, so I sent him home."** Expert opinion would suggest that it is important to observe the patient for 4 to 6 hours in the ED to assess for progression of symptoms.[11] Approximately 40% to 60% of patients end up being admitted for further observation of their symptoms.

3. **"I thought it was best to just monitor her. I never thought her airway swelling would progress and I wish I had set her up for a cricothyrotomy."** For emergency clinicians, airway assessment is the top priority in management of angioedema. If there is any concern for airway compromise, it is better to secure the patient's airway using typical airway devices. Otherwise, fiberoptic or surgical techniques may be necessary if edema progresses.

4. **"It couldn't be ACEI-induced angioedema, because that only happens when the patient starts taking the medication."** It is possible to develop ACEI-induced angioedema even after taking the medication for several years.[18] While the majority of cases occur within weeks of initiation, ACEIs should always be considered in patients presenting with first-time angioedema. It is prudent to have the patient stop taking the ACEI immediately and find a suitable alternative medication for management of blood pressure.

5. **"I didn't know that patients whose angioedema resolved in the ED needed further workup."** Given the risk for recurrence, all patients should be instructed to follow up with their primary care provider, even in the case of identifiable allergic triggers. In patients for whom no obvious trigger is identified, C4 levels should be sent from the ED or checked by their primary care provider.

6. **"The patient was older, so I thought it was very unlikely to be HAE."** While the majority of patients present within the first few decades of life with exacerbations of their HAE, approximately 20% to 25% of patients develop genetic defects that result in delayed presentations. Particularly if the patient has recurrent episodes, HAE should be considered.

7. **"I thought epinephrine was indicated only for allergic reactions and not for angioedema."** All causes of angioedema should be considered when initiating treatment, but allergic and immunologic reactions very frequently cause angioedema. Epinephrine should be considered as a therapeutic option, along with antihistamines and corticosteroids if an allergic source is likely.

8. **"I wasn't aware that angioedema affects the gastrointestinal tract."** Although rare, submucosal involvement of the gastrointestinal tract has been reported, especially in patients with HAE. This is often not considered as a potential source, so these patients may get repeated radiologic evaluations, and even surgical procedures that are not necessary. If identified, the patients can be treated with the properly targeted therapy and have improvement/resolution of their symptoms.

9. **"I thought tranexamic acid worked well in angioedema and was considered first-line."** Studies have shown that tranexamic acid is not as effective in HAE or ACEI-induced angioedema, and other therapies should be considered. When compared to no therapy, tranexamic acid may improve recovery time, but it should not be considered a first-line therapy.

10. **"I was surprised to learn pregnancy affects the presentation and management of HAE."** Physiologic changes in pregnancy can mitigate, aggravate, or have no effect on the patient's underlying HAE, so presentation severity can vary, compared to previous attacks. The preferred acute treatment of HAE attacks remains plasma-derived C1-INH, Berinert®, given IV at 20 units/kg. rhC1-INH and icatibant are generally not recommended for use in pregnancy or during periods of lactation unless alternatives are not available and the patient has significant or life-threatening edema.

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Time- And Cost-Effective Strategies

- Given that most cases of angioedema are secondary to a histamine-mediated cause, it is reasonable to empirically treat with antihistamines and corticosteroids in the case of the undifferentiated angioedema patient. These medications are largely safe, readily available, and are relatively inexpensive.
- Be sure that all patients who are evaluated for angioedema in the ED have close follow-up with their primary care provider; ideally, the next day. Good outpatient follow-up can lead to a shortened ED course, because this minimizes the need to have symptoms fully resolved by the time of discharge. With that said, the patient should be monitored frequently to ensure a "second worsening" effect is not occurring.
- In patients with a known history of HAE who present to the ED with generalized abdominal pain, it is reasonable to defer imaging if the patient has a history of similar prior episodes or has improvement in symptoms following therapy with a C1-INH.
- Complement blood testing can be obtained in the ED during an acute attack if the patient has a convincingly strong personal or family history to suggest HAE. While this will not change the patient's ED course, it has the potential to lead to a diagnosis sooner as testing is most sensitive during an acute attack.

5 Things That Will Change Your Practice

1. Be sure to consider HAE as a cause of abdominal pain. The rate of gastrointestinal involvement in HAE may be as high as 73%.
2. Avoid positive-pressure ventilation in a patient with angioedema; barotrauma will worsen airway edema.
3. Many patients with HAE will have symptoms in early childhood: the mean age of onset is thought to be between ages 5 and 11 years.[79] Emergency clinicians need to be aware of the differences in managing laryngeal edema in children.
4. ACEI-induced angioedema can occur hours to years after the initial dose of the drug. It is not an allergic reaction, it is a side-effect, and an alternative medication will need to be used.
5. According to Ishoo[42] and Das[43], patients with edema localized to the lips alone do not have an increased risk for intubation.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. **Hereditary angioedema is mediated by which of the following?**
   a. Cortisol
   b. Bradykinin
   c. Histamine
   d. Nephrin

2. **A patient with an unknown medical history presents to your ED with obvious edema to the lips, face, and hands. What is the most important next step in management of this patient?**
   a. Airway assessment
   b. Taking a thorough patient history with a full physical examination
   c. Beginning empiric treatment with epinephrine
   d. Beginning management with tranexamic acid

3. **Which sign or symptom is associated with airway compromise?**
   a. Facial swelling
   b. Tongue swelling
   c. Wheezing
   d. Stridor

4. **The best laboratory screen for hereditary angioedema (HAE) is:**
   a. Qualitative CI-INH levels
   b. Functional CI-INH levels
   c. C4 concentrations
   d. Tryptase concentrations

5. **Which subtype of angioedema would have a low C4, low C1-INH function, and normal to high C1-INH concentration?**
   a. HAE type 1
   b. HAE type 2
   c. Angiotensin-converting enzyme (ACE) inhibitor-induced angioedema
   d. Histamine-mediated angioedema

6. **Which medication used in the acute management of HAE is a specific inhibitor of the bradykinin B2 receptor?**
   a. Ecallantide
   b. Icatibant
   c. Recombinant C1-INH
   d. Plasma-derived C1-INH

7. **What percentage of patients with angioedema have their first attack by the age of 12 years?**
   a. 0 to 10%
   b. 20% to 40%
   c. 50% to 75%
   d. >90%

8. **Why is angioedema more life-threatening in the pediatric population?**
   a. Pediatric patients are more likely to develop an acute abdomen, compared to adults
   b. Children have a larger metabolic demand compared to adults
   c. Angioedema is rare in children, and is therefore not considered
   d. Smaller airway diameter compared to adults

9. **What is the preferred acute treatment of HAE in pregnant patients?**
   a. Epinephrine
   b. Corticosteroids
   c. Plasma-derived C1-INH
   d. Icatibant

10. **Which class of medication has a class I recommendation in the management of angioedema with evidence of anaphylaxis?**
    a. Epinephrine
    b. Corticosteroids
    c. Glucagon
    d. H1 receptor blockers

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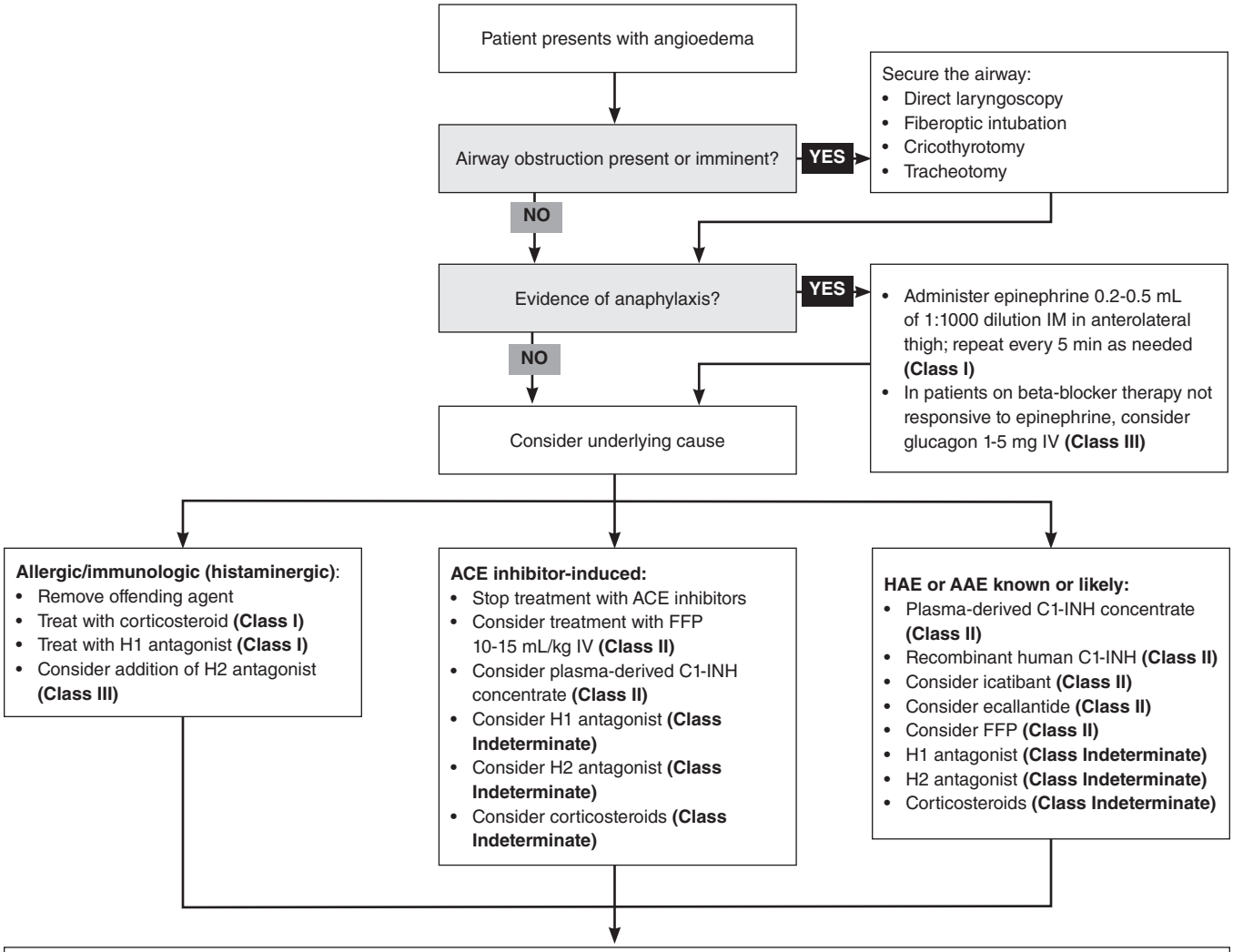
Clinical Pathway for Emergency Department Management of Patients With Angioedema


Patient presents with angioedema
Airway obstruction present or imminent?
YES
Secure the airway:
• Direct laryngoscopy
• Fiberoptic intubation
• Cricothyrotomy
• Tracheotomy
NO
Evidence of anaphylaxis?
YES
• Administer epinephrine 0.2-0.5 mL of 1:1000 dilution IM in anterolateral thigh; repeat every 5 min as needed (Class I)
• In patients on beta-blocker therapy not responsive to epinephrine, consider glucagon 1-5 mg IV (Class III)
NO
Consider underlying cause
Allergic/immunologic (histaminergic):
• Remove offending agent
• Treat with corticosteroid (Class I)
• Treat with H1 antagonist (Class I)
• Consider addition of H2 antagonist (Class III)
ACE inhibitor-induced:
• Stop treatment with ACE inhibitors
• Consider treatment with FFP 10-15 mL/kg IV (Class II)
• Consider plasma-derived C1-INH concentrate (Class II)
• Consider H1 antagonist (Class Indeterminate)
• Consider H2 antagonist (Class Indeterminate)
• Consider corticosteroids (Class Indeterminate)
HAE or AAE known or likely:
• Plasma-derived C1-INH concentrate (Class II)
• Recombinant human C1-INH (Class II)
• Consider icatibant (Class II)
• Consider ecallantide (Class II)
• Consider FFP (Class II)
• H1 antagonist (Class Indeterminate)
• H2 antagonist (Class Indeterminate)
• Corticosteroids (Class Indeterminate)
• Determine disposition based on severity of illness and response to treatment.
• Consider using Ishoo classification in determining appropriate disposition (see Table 4, page 15).

Abbreviations: AAE, acquired angioedema; ACE, angiotensin-converting enzyme; C1-INH, C1 esterase inhibitor; FFP, fresh frozen plasma; HAE, hereditary angioedema; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.
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QUICK READ

Points & Pearls

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Angioedema in the Emergency Department: An Evidence-Based Update

Points

- Angioedema can be acute or chronic, acquired or hereditary.
- Angioedema is broadly classified into 3 categories: (1) histamine-mediated, (2) bradykinin-mediated, and (3) idiopathic.[3]
- The patient's symptoms will help distinguish histamine- and bradykinin-mediated angioedema. **See Figure 2.**

Histamine-Mediated Angioedema

- Histamine-mediated angioedema is the most common form, accounting for 40% to 70% of ED presentations, and can be caused by environmental allergens or NSAIDs, opioids, and/or radiocontrast media.
- Histamine-mediated angioedema typically has a rapid onset, with urticaria.

Bradykinin-Mediated Angioedema

- Bradykinin-mediated angioedema is not triggered by an allergic reaction and may progress over hours to days.[11,21]
- Bradykinin-mediated subtypes include hereditary angioedema (HAE), ACE-inhibitor (ACEI)-induced angioedema, tPA-induced angioedema, and acquired angioedema (AAE).
- HAE has 2 primary subtypes: type 1, caused by a deficient level of C1-INH; and type 2, caused by decreased C1-INH function.[13]
- ACEI-induced angioedema is not an allergic reaction to the ACEI, but a side-effect.
- Symptoms of ACEI-induced angioedema can occur up to 10 years after the initial dose.[17]

Idiopathic Angioedema

- Idiopathic angioedema can be histamine-mediated or bradykinin-mediated.
- Histamine-mediated angioedema can be classified as idiopathic if the patient clinically responds to antihistamines and a workup for bradykinin-mediated etiology is negative.

Diagnosis

- HAE can be diagnosed by measuring C1-INH concentration and function. **See Table 2.**
- There is no routine laboratory test for ACEI-induced angioedema.[37] Diagnosis is by clinical presentation and history of ACEI use.

Pearls

- Airway patency should be assessed immediately, and the emergency clinician should have a low threshold to obtain a definitive airway.
- Edema can be worsened by positive pressure ventilation and over-manipulation.
- Intubation is likely to be technically challenging; it is recommended to have a dual-setup approach in the room.
- A general framework for preliminary diagnosis can be seen in **Figure 6**.
- Bradykinin-mediated angioedema has a slower course and is more probable in patients with a personal or family history of HAE and those refractory to first-line therapies, such as antihistamines.
- If swelling is localized to the gastrointestinal tract, presentation can mimic an acute abdomen.
- Be aware that 50%-75% of patients with HAE will have their first attack by the age of 12 years.[75]
- The Ishoo and Dass staging categories can be helpful in determining disposition. **See Tables 4, 5, 6, and 7**.

Treatment

- In histamine-mediated forms of angioedema, standard therapy for anaphylaxis is recommended.
- Antihistamines should be used as adjuncts to epinephrine.
- Corticosteroids have not been shown to be effective in histamine-mediated angioedema with or without anaphylaxis.[45,49] The potential benefits should be weighed against known side-effects.
- First-line therapy for bradykinin-mediated angioedema are C1-INH agents, bradykinin B2 receptor antagonists, and kallikrein inhibitors. **See Table 3** for agents, indications, and dosages.

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